

REGULATION OF GENETICALLY ENGINEERED (GE) ANIMALS

Written by Alison Van Eenennaam based on the FDA draft guidance for the regulation of genetically engineered animals (<http://www.fda.gov/cvm/Guidance/guide187.htm>)

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Are there any genetically engineered (GE) animal food products on the US market?

No. Despite the fact that the production of GE animals (animals modified by recombinant DNA (rDNA) techniques) with useful novel properties has been ongoing for approximately 25 years¹, as of September 2008 no GE food animal or animal-made pharmaceutical had received US regulatory approval. Although it should be noted that in 2006, the first human therapeutic protein, Antithrombin III (ATryn®, GTC Biotherapeutics, Framingham, MA), derived from the milk of genetically engineered goats was approved by the European Commission for the treatment of patients with hereditary antithrombin deficiency^{2,3}.

What GE animals are currently under development?

GE animals can be divided into broad classes based on the intended purpose of the genetic modification including: (1) to enhance food quality or agronomic traits (e.g., pigs with less environmentally deleterious wastes⁴, faster growing fish⁵); (2) to improve animal health (e.g., disease resistance^{6,7}); (3) to produce products intended for human therapeutic use (e.g., human therapeutic proteins have been produced in rabbits⁸, sheep^{9,10}, goats¹¹⁻¹⁴, pigs^{15,16}, and cattle¹⁷⁻¹⁹); (4) to develop animal models for human diseases²⁰ (e.g., pigs as models for cardiovascular diseases); and (5) to produce industrial or consumer products (e.g., spider silk fiber for multiple uses^{21,22}).

Are genetically engineered animals subject to premarket regulatory approval?

Yes. The Center for Veterinary Medicine (CVM) of the FDA has been working on applications submitted by developers of GE animals under the New Animal Drug provisions of the Federal Food Drug and Cosmetics Act (FFDCA). The FFDCA requires that each new animal drug be approved through a new animal drug application (NADA) based on a demonstration that it is safe and effective for its intended use. The rationale behind regulating GE animals using the new animal drug approach is based on the fact that the rDNA construct in a GE animal is intended to affect the structure or function of the body of the GE animals. Under this interpretation, the rDNA construct meets the FFDCA definition of a drug. Use of a new animal drug is unsafe unless the FDA has approved a NADA based on a demonstration that it is safe and effective for its intended use. All transgenic animals are subject to these premarket approval requirements.

The fundamental focus of the new animal drug regulatory approach is 1) Is the new animal drug safe for the animal? 2) Is the new animal drug effective, and 3) If the drug is for a food-producing animal, is the resulting food safe to eat? As many as two-dozen different human and animal drugs developed through transgenic animals have active applications on file with the FDA²³, and one company has announced it has filed a food application for a transgenic, growth-enhanced Atlantic salmon²⁴.

In September 2008 the U.S. Food and Drug Administration (FDA) released a draft guidance (<http://www.fda.gov/cvm/Guidance/guide187.htm>) for the regulation of GE animals. More information is available at the FDA website (<http://www.fda.gov/cvm/GEAnimals.htm>) including answers to common questions asked by consumers and the general public (<http://www.fda.gov/cvm/GEconsumersQA.htm>), and those pertinent to the developers of GE animals (<http://www.fda.gov/cvm/GEindustryQA.htm>).

Is Investigational Research with Genetically Engineered Animals Regulated?

Yes. To obtain FDA regulatory approval, developers of genetically engineered animals must first submit an Investigational New Animal Drug (INAD) exemption to allow them to conduct investigational research on a new type of genetically engineered animal. During this investigational phase, a single INAD file may be established on investigational lines of GE animals derived from different transformation events (i.e. animals that contain different numbers of rDNA constructs at different locations in the genome) prior to establishing the specific event intended for commercialization. Because the site at which an rDNA construct is located can affect both the health of the animal and the level and control of expression of the construct (i.e., its effectiveness), in general, each animal derived from a separate transformation event will be considered to contain a separate new animal drug and will be evaluated independently as the basis for a new animal drug approval.

It should also be noted that developmental stage research with transgenic food animals is subject to the existing animal welfare regulations that govern animal research. All entities receiving or applying for federal funding to carry out research using animals are required by The Animal Welfare Act, a federal law which was passed in 1966, to have a program overseen by a committee identified as the Institutional Animal Care and Use Committee (IACUC) to review research protocols involving warmblooded animals and domestic livestock species used in nonagricultural research and teaching. The Animal Welfare Act is administered through the United States Department of Agriculture (USDA) and is enforced through unannounced inspections by a USDA Veterinary Medical Officer.

What is involved in obtaining a new animal drug approval (NADA) for genetically engineered animals?

When submitting a NADA the developer must show that the new animal drug is safe and effective for its intended use. The FDA has provided guidance for data submission to help guide sponsors of genetically engineered animals through the regulatory submission process. The seven steps identified and briefly outlined below give an indication of the type of information the FDA requires to approve a genetically engineered animal new animal drug application.

1. *Product Identification*: a broad statement characterizing the GE animal and the claim being made for the GE animal;

The identification of the product sets the context for the regulatory review. What is the GE animal (i.e. what species and rDNA construct combination that is being proposed) and what is the purpose (i.e., intended use) of the rDNA that is the subject of the NADA. For example, the cows on the left have been genetically engineered to inactivate the prion protein responsible for bovine spongiform encephalopathy (BSE) or mad cow disease. Photo from Richt et al.⁷



2. *Molecular Characterization of the Construct*: a description of the rDNA construct and how it was made;

3. *Molecular Characterization of the GE Animal Lineage*: a description of the rDNA construct that was introduced into the animal, and whether it is passed to the offspring in a predictable way;

This step requires the provision of data detailing the method by which the rDNA construct was introduced into the animal, including whether the initial GE animal was chimeric. In addition, the breeding strategy used to produce the lineage progenitor (the GE animal that contains the final stabilized version of the initial event and from which the GE animals intended to enter commerce are derived) should be described and the final stabilized rDNA construct in the GE animal should be characterized.

4. *Phenotypic Characterization of GE Animal*: information describing the GE animal, including comprehensive data on the health of the animal;

The previous steps of the review process have concentrated on establishing and characterizing the rDNA construct and its integration into the resulting GE animals. Information in this and the following steps helps establish whether the GE animal poses any risks to humans, risks to health of the GE animal, or risks to the environment. Data collected here will include whether the rDNA construct or its expression product(s) cause any direct or indirect toxicity including information about the health of the GE animals, including veterinary and treatment records, growth rates, reproductive function, and behavior.

5. *Genotypic and Phenotypic Durability Assessment*: demonstrates that the offspring (over multiple generations) continue to inherit the rDNA construct and that they continue to express the new trait

This step is intended to provide information to ensure that the rDNA construct in the GE animal resulting from the specific transformation event and defining (identifying) the GE animal being evaluated is durable (i.e. that there is a reasonable expectation that the rDNA construct is stably inherited, and the phenotype is consistent and predictable).

6. *Food/Feed Safety and Environmental Safety Assessments*: the assessment of any environmental impacts, and for GE animals intended for food, that food from those GE animals is safe to eat for humans and/or animals

Food/Feed Safety

This part of Step 6 focuses on the issue of whether food or feed derived from a GE animal is safe for humans or animals consuming edible products from the animals. The risk issues involved in determining food and feed safety can be divided into two overall categories. The first addresses whether there is any direct toxicity, including allergenicity, via food or feed consumption of the expression product of the rDNA. The second category addresses potential indirect toxicity associated with both the rDNA and its expressed product (e.g., whether location or expression of the rDNA affects physiological processes in the resulting animal such that unintended food/feed consumption hazards are created, or whether existing food/feed consumption risks are increased).



In the end, if the expression product(s) is shown to be safe, and the composition of edible tissues from the GE animal is shown to be as safe as those from animals of the same or comparable type that are commonly and safely consumed, then we expect to view this as evidence that food and feed derived from the GE animal is safe (i.e., there is a reasonable certainty of no harm from consumption of the food or feed).

Environmental Safety

Actions on INADs are considered federal actions under the National Environmental Policy Act (NEPA), and as such may require preparation of an environmental assessment (EA) or environmental impact statement (EIS). Through the preparation of an EA or EIS, FDA will examine the potential for environmental impacts, including the potential for inadvertent release or escape of the GE animal and/or its products into the environment, and whether certain measures may mitigate any potential significant impacts that would adversely affect the human environment. Additionally, sponsors may be subject to applicable environmental requirements with respect to runoff from animal production facilities and land receiving animal waste under the Clean Water Act. Although action on an INAD and, in many cases, action on a NADA, is typically categorically excluded from the requirement to prepare an EA, the FDA expects that at least initially, most GE animal applications would have to be evaluated to determine whether such an application individually or cumulatively affects the environment. If an EA finds that the GE animal will have no significant impact (FONSI), then the NEPA requirements will have been fulfilled. If the EA finds a significant impact, then the evaluation will proceed to the preparation of an EIS.

7. *Effectiveness/Claim Validation*: a demonstration that the GE animal has the characteristics that the developer says it has.

The previous steps of the review process primarily addressed identity and safety issues. This last step of pre-market review addresses effectiveness, i.e., whether data validates claims for the characteristics that the GE animal is intended to exhibit. For example, if a GE animal is intended to resist disease, it should be demonstrated that the GE animals are indeed resistant to that disease. In the case of GE animals that are intended to produce a non-food product, data needs to demonstrate that the animal indeed produces the claimed product. If that product is intended for human therapeutic use, the safety and effectiveness of that drug would be evaluated separately by Center for Drug Evaluation and Research.

Are there any genetically engineered food animals that are currently being commercialized for human consumption?



In the United States, there is a line of transgenic growth enhanced Atlantic salmon that is under review by the FDA for commercialization in aquaculture operations. Created by Aqua Bounty Technologies, a biotechnology company focused on improving productivity in commercial aquaculture, the *AquAdvantage* Atlantic salmon reach market size twice as fast as wild-type salmon (pictured right). Consisting of an “all fish” construct, the transgenic salmon contain an ocean pout antifreeze promoter driving a Chinook salmon growth hormone gene that allows the fish to grow up to 6 times larger than non-transgenic salmon of the same age²⁵. Aqua Bounty has already completed a critical FDA requirement,

characterizing the molecular “all fish” DNA construct²⁴. All major studies required to gain approval for the transgenic salmon to be consumed in the US, such as food safety, allergenicity, nutrient content and genetic stability through inheritance, have been completed and are under review by the FDA.

What is Enforcement Discretion?

FDA may exercise “enforcement discretion” over some GE animals, based on their potential risk and on a case-by-case basis. This means that the agency may not require premarket approval for a low-risk animal. Two principal examples are GE animals of non-food species that are regulated by other agencies (e.g. insects that are under United States Department of Agriculture APHIS oversight), and



GE animals of non-food species that are raised and used in contained and controlled conditions (e.g. GE laboratory animals used in research institutions).

Other applications may also be allowed to come to market without a NADA based on an evaluation of risk factors, as was done following the receipt of information about Zebrafish aquarium fish (Glofish) genetically engineered to express colored fluorescent proteins that glow in the dark (<http://www.fda.gov/bbs/topics/NEWS/2003/NEW00994.html>).

Where FDA exercises enforcement discretion over the INAD or NADA requirements, no review of environmental risks under the National Environmental Policy Act (NEPA) would take place. As a result, environmental risks would be among the factors considered in determining whether to exercise enforcement discretion. FDA does not expect to exercise enforcement discretion for animal species traditionally consumed as food.

Will food from genetically engineered animals be labeled or specially identified?

Food from GE animals is subject to the same labeling product-based requirements as other foods (i.e. the labeling of foods is not required unless there has been a significant change in the nutritional attributes or other chemical characteristic compared to conventional counterpart). In situations in which food from a GE animal is materially different from that of its non-engineered counterpart, for example if it has a different nutritional profile, then that information that would have to be revealed in labeling. However, Marketers may voluntarily label their foods as coming from GE or non-GE animals, as long as the labeling is truthful and not misleading. FDA has oversight of labeling of fish and seafood, of milk and other dairy products, and of whole eggs in their shells. The U. S. Department of Agriculture’s Food Safety and Inspection Service (FSIS) ensure that the proper labels are used for meat, poultry, and other egg products.

Will GE animals developed to produce products intended for human therapeutic use end up in the food supply?

Without FDA approval for food use, it would be illegal for a company producing human therapeutic products in GE animals to direct any of its GE animals into the food supply. In general, such animals would not be intended for food use: they are engineered to produce a therapeutic substance, and their value is in that product and not the meat or milk from the animal. Given the large amount of food safety data that would be required to be provided to FDA for each GE animal line intended to enter the food supply, and the kind of food safety issues that pharmaceutical chemicals present in such animals would generally pose, it would be very unusual for developers of these animals to want to enter their animals into the food supply. It is much more likely that these animals will be disposed of in a way that does not involve human food use when they have reached the end of their lives. However, if a developer provided sufficient evidence of safety and the FDA approved the animal for food use, then the decision on whether to enter it into the food supply would be a marketing issue for the food producer and the developer and not a food safety issue for the public.

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